REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and foregoing arguments is respectfully requested.

Claims 21-37 are pending. Claims 21-34 and 37 are under consideration. Claims 21-34 have been amended and claim 37 has been added, as explained below. No new matter has been added as a result of these amendments.

Claim Objection

Claims 25-34 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. Applicant has deleted the multiple dependency from the claims. Withdrawal of the objection to claim 25-34 for this informality is respectfully requested.

Rejection of Claims 21-34 Under 35 U.S.C. § 112, Second Paragraph

Claims 21-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner points out that the claims are indefinite for a number of reasons (A-K) which are addressed herein.

A. It is not clear what additional oligonucleotide is being added from the recitation "adding an additional oligonucleotide" in steps ab) and bb) of claim 21. Applicant has amended these steps to recite "adding an additional oligonucleotide separate from the oligonucleotide of aa)" (or "bb)" for step bb)). Therefore, the claims clearly recite that the additional oligonucleotides that are added are separate from those previously recited.

B. It is not clear what, if any, structural limitations are being imposed on the oligonucleotide that cause its inability to bind to the matrix from the recitation "cannot bind to the matrix" in steps ab) and bb) of claim 21. Applicant submits that this language is clear and definite as the oligonucleotide has a structure that prevents it from binding to the matrix. The claims are directed to a method instead of a composition and do not require the oligonucleotide to be defined by its structure.

C. There is insufficient antecedent basis for "the orientation determined" in steps ac), bc) and c) of claim 21. Applicant has amended this claim to recite "an orientation determined" in these steps.

D. There is insufficient antecedent basis for "the blockage" in steps ac), bc) and c) of claim 21. Applicant has amended this claim to recite "a blockage" in these steps.

E. There is insufficient antecedent basis for "the ends" in steps ac), bc) and c) of claim 21 and "their ends" in claim 31. Applicant has amended claim 21 by deleting "the" in these steps and deleted "their" in claim 31. Furthermore, the Examiner states that it is unclear if the claims are referring to each and every end of both oligonucleotides, or only one end of each oligonucleotide (the end without the recognition sequence). Applicant has amended claim 21 to recite "ends of the oligonucleotides from steps aa) and ab) that are not ligated" for step ac) (and accordingly for steps bc) and c)). Applicant submits that the claims clearly recite that one end of the the oligonucleotides from the respective steps are blocked and that the oligonucleotides are ligated in an orientation determined by these blocked ends that are not ligated.

F. There is insufficient basis for "reactants" in the recitation "removing non-consumed reactants and enzymes" in steps ad), bd) and d) of claim 21. Additionally, the Examiner states that it is not clear when the reactants and enzymes were added, and which reactants and enzymes will be considered as "non-consumed". Applicant has amended these steps to recite "removing oligonucleotides from steps

aa), ab) and ac) that are not coupled or ligated" for step ad) (and accordingly for steps bd) and d)). Therefore the claims are now clear and definite as to what is removed.

G. There is insufficient basis for "the reaction mixture" in steps af), bf) and f) of claims 21 and 24, and it is not clear what exactly is the "reaction mixture". Applicant has deleted "the reaction mixture" and amended step af) to recite "separating the type IIS restriction enzyme and the shorter oligonucleotide from the elongated oligonucleotide obtained in step ae). Additionally, in order to provide antecedent support, Applicant has amended step af) to recite "and resulting in an elongated oligonucleotide and a shorter oligonucleotide". Steps bf) and f) of claim 21 are also amended in a similar manner. Claim 24 has been amended to delete "reaction mixture" and the recitation "type IIS restriction enzyme, the shorter oligonucleotide, the unreacted exonuclease and the unreacted phosphatase" has been added therefor. Support for the separation of the elongated oligonucleotide from the shorter oligonucleotide and other reactants as claimed can be found in figure 1 of the specification. Therefore the claims are now definite as to what is separated and removed.

H. There is insufficient basis for "the elongated oligonucleotide from step aa) obtained in step ae)" in steps af), bf) and f) of claim 21. Additionally, the Examiner states that it is not clear how the oligonucleotide can be derived from step aa) and obtained in steps ae), and which oligonucleotide Applicant is referring to here. The phrase "from step aa)" in step af) (and respective language from steps bf) and f)) has been deleted. The claims have been amended as indicated in "G" above to provide antecedent basis for "the elongated oligonucleotide" and which oligonucleotide Applicant is referring to here.

I. Claim 22 is indefinite because it is not clear how the product of claim 21 can be also used as a required reagent in the preliminary steps of

the same claim. Claim 22 has been amended to now recite "A method for the production of a nucleic acid molecule wherein an oligonucleotide is produced from the method of claim 21, step f), and is used in an additional method of claim 21 in step ab) or bb)". Applicant submits that the claim clearly recite that the oligonucleotide produced in claim 21 is used in a method according to claim 21 again in step ab) or bb).

J. Claims 33-34 are indefinite in view of the recitation "wherein the various type IIS restriction endonucleases are replaced by ribozymes" since claim 21 requires type IIS enzymes. The Examiner suggests using alternative languages in the claim. Claim 33 has been amended to recite "wherein in step gb) ribozymes are used instead of type IIS restriction enzymes which cleave in an analogous manner as compared to the type IIS restriction enzymes". Applicant submits that the claim is clear as it uses alternative language. Applicant thanks the Examiner for her suggestion.

K. Claims 29-34 are indefinite since claim 29 recites a limitation within a limitation. Claim 29 has been amended to remove this recitation. The narrower limitation has now been added in new claim 37.

Applicant has addressed every indefiniteness pointed out by the Examiner. For these reasons, Applicant respectfully requests withdrawal of the rejection of claims 21-34 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 21-27, 29-32 and 34 Under 35 U.S.C. § 103(a)

Claims 21-27, 29-32 and 34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 (herein "DuBridge") in view of Church *et al.,* U.S. Patent No. 6,485,944 (herein "Church"). Applicant respectfully traverses the rejection.

The Examiner states that the prior art has been applied in view of the indefiniteness rejections as best as the Examiner can understand the invention being claimed. Applicant has amended the claims such that the claims are now

definite and clear. Accordingly, the claims are patentable over DuBridge in view of Church as explained herein.

Applicant's invention is directed to a method for the production of a nucleic acid molecule, the nucleic acid molecule being assembled by a series of steps that join oligonucleotides together, forming a longer oligonucleotide in the process and ultimately, the nucleic acid molecule (pages 2-5 of the specification). Applicant's invention provides for the efficient synthesis of double-stranded DNA fragments of any sequence and length. This synthesis is based on a method that allows parallel synthesis and sequence-independent linkage of any gene fragment. It is also simplistic such that the method can be automated (page 2, second paragraph).

DuBridge discloses an adaptor-based sequence analysis for analyzing nucleic acids, and more specifically for analyzing terminal nucleotides of polynucleotides by specific ligation of labeled adaptors (col. 1, lines 4-7). The problem which DuBridge wishes to solve is dealing with the ends of polynucleotides or adaptors that are capable of self-ligation, as illustrated in Figure 1 (col. 1, lines 40-44). Thus, DuBridge's method prevents self-ligation of the polynucleotides (col. 1, lines 64-66). Therefore, the object of DuBridge's invention is to provide an adaptor-based analysis method in which neither the adaptors nor target polynucleotides self-ligate (col. 2, liness 2-4). DuBridge's focus of the invention is the removal of the 5' phosphate from the end of the polynucleotide to be analyzed so that self-ligation cannot occur (col. 2, lines 21-24).

Figure 2a of DuBridge illustrates a method for determining the identity of nucleotides at the terminus of a polynucleotide (col. 2, line 50 to col. 3, line 8). The steps described therein do not include a step of keeping an elongated oligonucleotide while washing away the shorter oligonucleotide, as claimed by Applicant in steps ae), af), be), bf), d) and f) in claim 21. See the above discussions for (G). In fact, Figure 2a of DuBridge shows that a shorter oligonucleotide is the end product. Although DuBridge discloses a repeated cycle of ligation and cleavage somewhat similar to Applicant's method, and uses

restriction enzymes as claimed by Applicant, the repeated cycles are used for identification of nucleotides of a target polynucleotide resulting in a shorter oligonucleotide (col. 3, lines 9-23). Applicant's claims are directed to creating a larger oligonucleotide ("an elongated oligonucleotide" which is retained in the process).

Note that figures 3a-3e of DuBridge illustrate an embodiment for DNA sequencing that does not require cycles of ligation and cleavage (col. 3, lines 61-64).

The Examiner cites col. 13 and 14, where it is disclosed that adaptors such as A1, A2 and A3 are added and ligated for step ab) and other steps as claimed in claim 21. However, col. 15, lines 9-27 of DuBridge discloses two significant features that distinguish DuBridge's method from the Applicant's claimed method. Here it is disclosed that DuBridge's adaptors (oligonucleotides) are ligated and then attached to the solid supports (solid matrix) (col. 15, lines 9-12). Conversely, Applicant's method requires at least some oligonucleotides to be attached to a solid matrix before ligation (steps aa) and ba)). At col. 15, lines 12-14, it is also disclosed that the oligonucleotides used in DuBridge's method are rendered single stranded and "stripped". Thus, it appears that the retained oligonucleotide is a ultimately shortened whereas Applicant's method successively lengthen an oligonucleotide through repeated ligation. Although the Examiner attempts to "read" the method of DuBridge into the claims, DuBridge does not meet the claimed method since DuBridge does not disclose a method having a series of ordered steps as claimed. The Examiner has attempted to piecemeal the steps disclosed throughout DuBridge to meet the claim language, but this piecemeal does not meet the ordered series of steps as claimed.

The Examiner states that Dubridge does not disclose step bg) of claim 21, wherein the oligonucleotide linked to the solid support is cleaved using type IIS restriction enzymes and provides Church as a teaching for such. However, Applicant submits that Church does not cure the deficiencies of DuBridge as stated above. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 21-27, 29-32 and 34 under 35 U.S.C. § 103(a) as being

unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 in view of Church *et al.,* U.S. Patent No. 6,485,944.

Claim 28 is rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 (herein "DuBridge") in view of Church *et al.,* U.S. Patent No. 6,485,944 (herein "Church") as applied to claim 21, and further in view of Lane *et al.,* U.S. Patent No. 5,770.365 (herein "Lane").

The Examiner cites Lane as a teaching for modification of the oligonucleotide of step aa), ba) or a) via coupling a loop region to the solid matrix. However, Lane does not cure the deficiencies of DuBridge and Church as stated above. Applicant's arguments above are incorporated herein. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 28 under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 in view of Church *et al.,* U.S. Patent No. 6,485,944, and further in view of Lane *et al.,* U.S. Patent No. 5,770,365.

Claim 33 is rejected under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 (herein "DuBridge") in view of Church *et al.,* U.S. Patent No. 6,485,944 (herein "Church") as applied to claim 21, and further in view of Israel, U.S. Patent No. 5,981,190.

The Examiner cites Israel as a teaching for using ribozymes instead of type IIS restriction enzymes. However, Israel does not cure the deficiencies of DuBridge and Church as stated above. Applicant's arguments above are incorporated herein. Accordingly, Applicant respectfully requests withdrawal of the rejection of claim 33 under 35 U.S.C. § 103(a) as being unpatentable over DuBridge *et al.,* U.S. Patent No. 5,888,737 in view of Church *et al.,* U.S. Patent No. 6,485,944, and further in view of Israel, U.S. Patent No. 5,981,190.

CONCLUSION

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. Sections 112 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,

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